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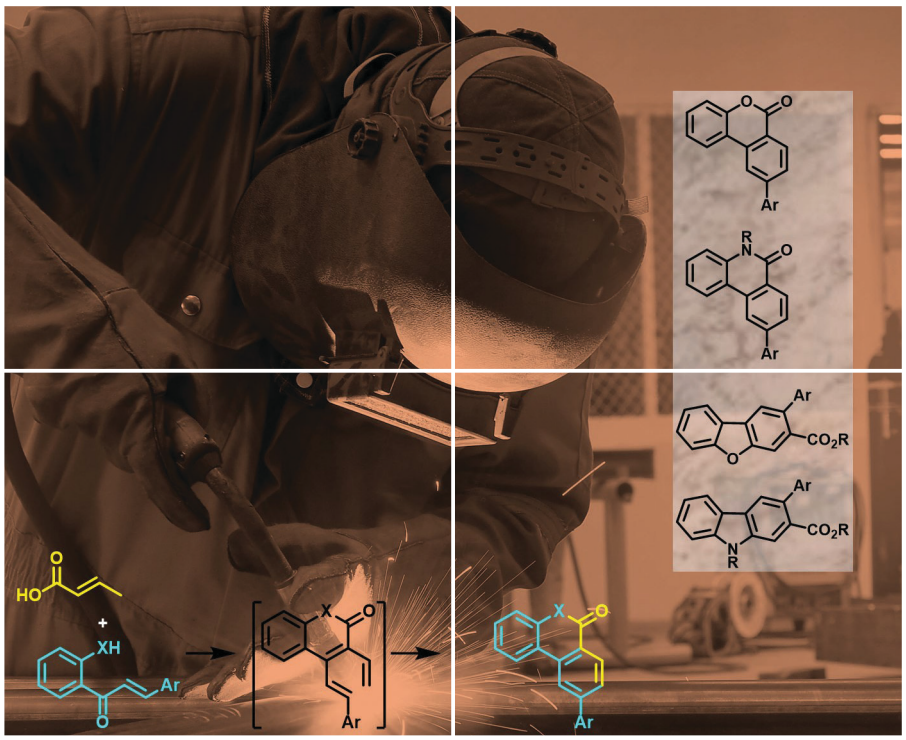

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A metal-free aromatic cascade for the synthesis of diverse heterocycles†

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A metal-free aromatic cascade has been developed for the synthesis of diverse heterocycles from readily accessible hydroxy/aminochalcones and acid/alkyl halides. The cascade is initiated by a base-mediated intramolecular aldol cyclization/dehydration sequence to provide a triene, which sets the stage for a 6π-electrocyclization/oxidative aromatization to access diverse heterocyclic scaffolds.

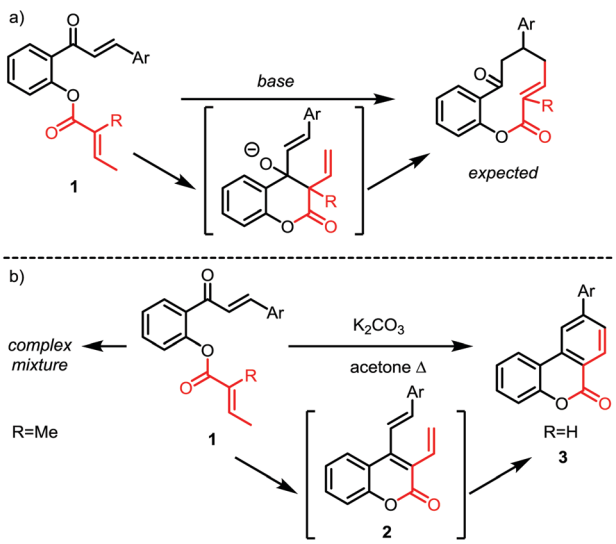
Cascade reactions are an elegant strategy for assembling complex molecules in organic synthesis.[1] Delivering high efficiency and atom economy, cascade reactions use multiple transformations in a one-pot fashion.[2] Employing cascade reactions as an approach eases reaction workup, purification, time, and waste management.[3] These advantages altogether make cascade reactions ideal for green chemical synthesis.[4]

In continuing our work on cascade approaches for medium-sized scaffolds,[5] we designed a metal-free cascade comprising an intramolecular aldol reaction/anionic oxy-Cope rearrangement to furnish 10-membered lactones (Scheme 1a). The cascade precursor is readily accessible through the standard coupling of hydroxychalcones to unsaturated acids. However, when we exposed precursor **1** (R = Me) to basic conditions, we recovered a complex mixture of products. We suspected that the additional methyl group dissuaded the desired enolization, leading to ketene formation and subsequent fragmentation of the hydroxychalcone component.[6] When the methyl group was removed (R = H), we did not observe any trace of the desired macrolactone, but small quantities of the aromatized benzo[*c*]coumarin **3**, which was presumably formed *via* an intramolecular 6π-electrocyclization of 1,3,5-triene **2** (Scheme 1b).[7]

Although there are examples in the literature of 6π-electrocyclization employed in the synthesis of biologically relevant natural products,[8] this serendipitous cascade represents a unique approach for the construction of functionalized benzo[*c*]coumarins that does not rely on modification of a pre-formed coumarin scaffold.[9]

Inspired by these results, we envision applying this approach to the synthesis of heterocyclic scaffolds, which are found in numerous natural products and drug molecules. In particular, the benzo[*c*]coumarin core can be found in several natural products, and has recently been used as a precursor to access the cannabinoid receptor agonist cannabinol.[10d] In addition, the related heterocycles such as phenanthridin-6(5*H*)-ones, dibenzofurans, and carbazoles are also commonly found in nature and are medicinally relevant compounds (Fig. 1).[10]

Although there are multiple methods currently available in the literature for the synthesis of these heterocycles, most rely on the use of transition metal catalysts.[11] With high cost and difficult purification, reducing the use of expensive transition



Scheme 1 (a) Anionic oxy-Cope approach to 10-membered macrolactones. (b) Serendipitous approach to benzo[*c*]coumarins.

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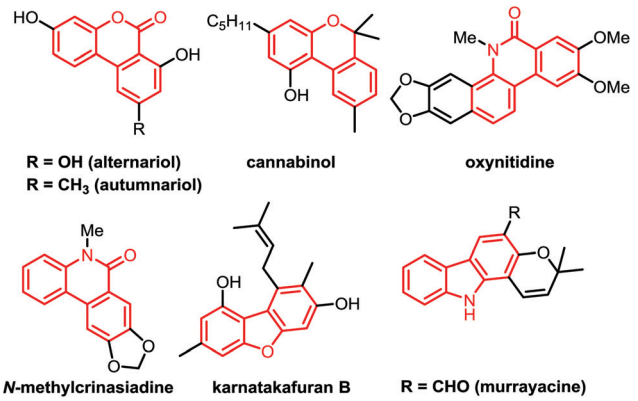


Fig. 1 Aromatic heterocycles in natural products.

metal catalysts in chemical reactions is a unifying goal in the synthetic community.[12] Keeping these advantages in mind, our serendipitous cascade is attractive and provides an alternative metal-free method for the synthesis of aromatic heterocycles.

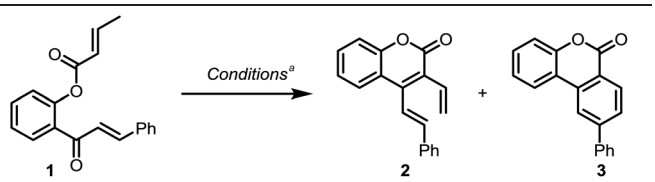
We commenced our reaction optimization for the formation of benzo[*c*]coumarin **3**. When precursor **1** was exposed to K_2CO_3 in refluxing acetone for 16 hours, we observed complete conversion of **1** to triene **2**, with further conversion to **3** (Table 1, entry 1). These reaction conditions however resulted in a low overall yield of **3**. We then attempted the reaction utilizing organic bases, beginning with Et_3N. After 16 hours of stirring at reflux temperature in dichloromethane, we observed no conversion to triene **2** and pure **1** was recovered (entry 2). When a stronger base (DBU) was utilized, we observed full conversion of **1** to furnish a mixture of **2** and **3** (entry 3). Inspired by recent reports on the 6π-electrocyclization of 1,3,5-triene systems,[9] DMSO was employed as the reaction solvent, and improved conversion of **2** to **3** was observed (entry 4). When the reaction mixture was heated to 80 °C in DMSO, full conversion of **2** to **3** was observed, with an isolated yield of 82% (entry 5).

The reaction was also successful using lower quantities of the base; however, a notable decrease in the isolated yield was observed (entries 6 and 7) with a longer reaction time. When 0.1 equivalents of base were utilized, an incomplete conversion of **1** was observed, and **3** was obtained in trace quantity (entry 8).

With optimized conditions in hand, we turned our attention towards the substrate scope for this cascade (Fig. 2). The reaction was amenable for substituents on the pre-existing aromatic ring, resulting in good yields of compounds **3b** and **3c**. Next, we explored the electronic influence of the triene on the overall reaction cascade. Electron-neutral and electron-donating substituents were well-tolerated and resulted in good to excellent yields (**3d–3f**). The reaction though was low-yielding with the trifluoromethyl-substituted compound **3g**. Reaction conditions were also tolerant of other heterocycles comprising the chalcone component, and furan-substituted **3h** was synthesized in good yield. Finally, a lower yield was observed for the methyl-substituted compound **3i**, and in this instance, we observed byproducts arising from incomplete electrocyclization in the crude NMR.

Addressing a limitation in some of the current electrocyclization-based methods for benzo[*c*]coumarin formation, we wondered whether our method was suitable for synthesizing their nitrogen analogues, phenanthridin-6(5*H*)-ones (Fig. 3).[9a] By coupling *N*-alkylaminochalcones to crotonyl chloride, we were able to access precursors **4** in a three-step sequence. The

Table 1 Reaction optimization for the aldol elimination/electrocyclization sequence



Entry	Base (equiv.)	Solvent	Temp.	2/3 [b]
1	K_2CO_3 (3.0)	Acetone	Reflux	1 : 2 (23)[c]
2	Et_3N (3.0)	DCM	Reflux	N.R.
3	DBU (3.0)	DCM	rt	95 : 5
4	DBU (3.0)	DMSO	rt	90 : 10
5	**DBU (3.0)**	**DMSO**	**rt → 80 °C**	**0 : 100 (82)[c]**
6	DBU (2.0)	DMSO	rt → 80 °C	0 : 100 (64)[c]
7	DBU (1.0)	DMSO	rt → 80 °C	0 : 100 (45)[c]
8	DBU (0.1)	DMSO	rt → 80 °C	Trace

[a] All optimization reactions were performed by adding a base at room temperature to a solution of **1** in DMSO (0.15 M). The reaction vessel was sealed and heated at the indicated temperature for 16 hours. [b] The percent ratio of **2** and **3** was determined by crude ^{1}H NMR integration. [c] Isolated yield of **3** obtained after column chromatography. N.R. = no reaction.

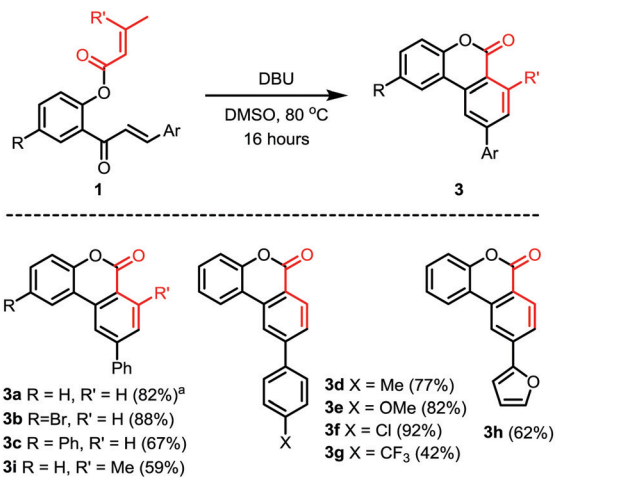


Fig. 2 Scope of benzo[c]coumarin substrate examples; all reactions were performed by adding DBU (3.0 equiv.) to a 0.15 M solution of **1** (1.0 equiv.) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction mixture was heated to 80 °C for 16 hours. [a]Reaction was also performed on a 1-gram scale with an isolated yield of 76%.

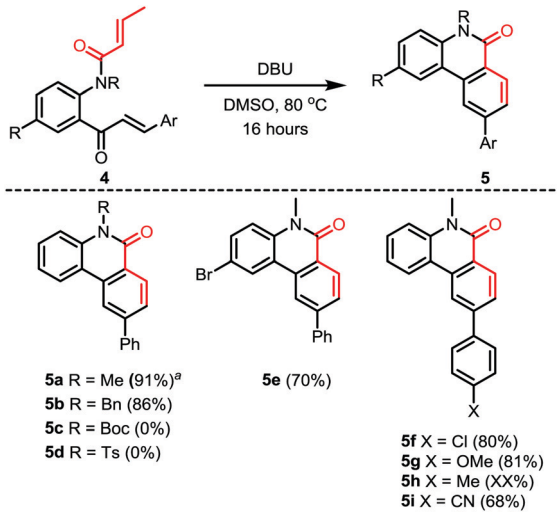


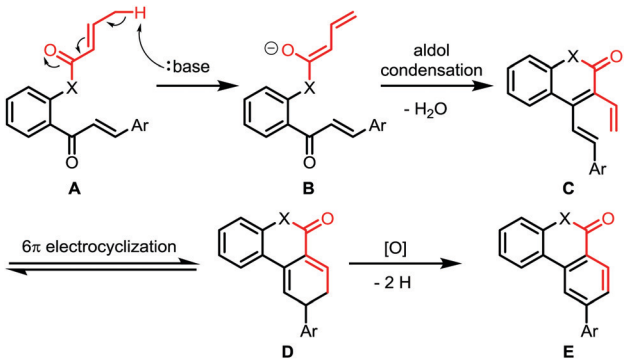
Fig. 3 Scope of phenanthridin-6(5*H*)-one substrate examples; all reactions were performed by adding DBU (3.0 equiv.) to a 0.15 M solution of **1** (1.0 equiv.) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction mixture was heated to 80 °C for 16 hours. [a]Reaction was also performed on a 1-gram scale with an isolated yield of 89%.

parent compound **5a** was synthesized in excellent yield, and notably, was suitable for a 1-gram scale-up, with only a slight decrease in the overall yield (89%). The reaction also tolerated other *N*-protecting groups well, with benzyl-protected **5b** synthesized in comparable yield. Alkyl protection of the amide was crucial to the success of this reaction; however, when the free N–H amide was exposed to the optimized DBU heating conditions, a complex mixture of products was recovered. Similarly, the reaction conditions were not suitable for the common nitrogen protecting groups *tert*-butylcarbamate (boc) and the tosyl group.[13] In both the cases, cleavage of the crotonylamide bond was observed at room temperature, resulting in the recovery of the corresponding aminochalcone precursor.

Like their oxygen-containing counterparts, the cascade was tolerant of electron-neutral and electron-donating substituents (**5f–5h**). Again, we observed diminished yields with electron-withdrawing substituents, with cyano-substituted **5i** synthesized in only moderate yields. We observed higher yields overall for the synthesis of these phenanthridin-6(5*H*)-ones, presumably due to the disfavoured ketene-mediated fragmentation of **4**, relative to **1**, in the presence of a strong base.[6]

A plausible reaction mechanism for this cascade is shown in Scheme 2. First, γ-deprotonation of crotonate **A** generates enolate **B** which undergoes an α-enolate attack on the ketone followed by the loss of water to generate 1,3,5-triene **C**. Under heating conditions, triene **C** can undergo a 6π-electrocyclization forming **D**, which is capable of aromatization *via* an aerial oxidation,[14] generating benzocoumarin or phenanthridinone **E**.

Several experiments were performed to validate the proposed reaction mechanism. We were able to isolate triene **C** after 90 minutes of stirring at room temperature in the presence of DBU. When triene **C** is exposed to the same DBU conditions while heating to 80 °C for 16 hours, **E** is obtained in good yield supporting our proposal that it is an intermediate in this process. It was also found that the addition of the single electron oxidant DDQ can promote the oxidation of **D** to **E**. We then probed whether the reaction cascade could be accomplished *via* direct α-enolization of esters **1**, instead of indirect γ-enolization. When hydroxychalcone was coupled to vinylacetic acid, we observed complete olefin isomerization to give exclusively α,β-unsaturated product **1a**.



Scheme 2 Proposed mechanism for the formation of benzo[*c*]coumarins and Phenanthridin-6(5H)-ones.

Fortunately, when hydroxychalcone was coupled to various arylacetic acids, we were able to isolate esters **6** in good yields (Fig. 4). These substrates tolerated α-enolization well and underwent the desired aldol elimination/6π-electrocyclization cascade at 120 °C to provide heterocycles **7a–7d** in yields ranging from good to excellent. The reaction conditions were also suitable for the formation of phenanthridinones **7e** and **7f**. Unfortunately, phenyl- and pyridine-substituted **6g** and **6h**,

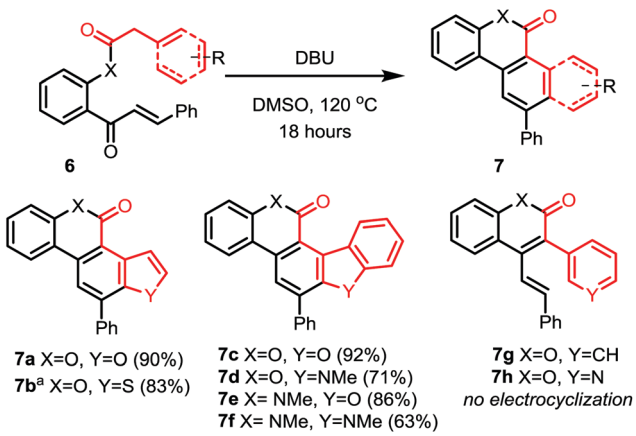


Fig. 4 Scope of the electrocyclization cascade incorporating an aryl component; all reactions were performed by adding DBU (3.0 equiv.) to a 0.15 M solution of **1** (1.0 equiv.) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction mixture was heated to 120 °C for 16 hours. [a]Compound was prone to intramolecular aldol elimination under coupling conditions and the reaction was performed using the corresponding triene.

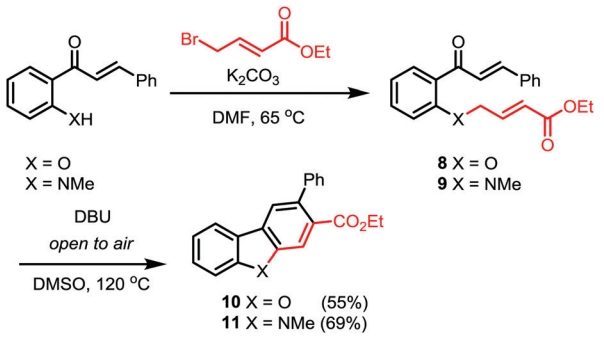


Fig. 5 Aldol/electrocyclization route to carbazoles and dibenzofurans; all reactions were performed by adding DBU (3.0 equiv.) to a 0.15 M solution of **1** (1.0 equiv.) in DMSO at room temperature. After stirring for 90 minutes at room temperature, the reaction mixture was heated to 120 °C for 16 hours.

respectively, did not undergo electrocyclization after triene formation, even when the reaction temperature was elevated to 180 °C.

Lastly, we turned our attention towards accessing other benzannulated heterocyclic scaffolds, namely dibenzofurans and carbazoles (Fig. 5). By changing the chalcone coupling partner to ethyl 4-bromocrotonate, compounds **8** and **9** were prepared. We envision that when exposing to a base, they could undergo enolization *via* γ-deprotonation, and unlike their **1** and **4** counterparts, act as nucleophiles from the γ-position as opposed to the α-position, setting the stage for the 6π-electrocyclization step. Indeed, when **8** and **9** were exposed to the optimized DBU heating conditions, **10** and **11** could be isolated in good yields. Notably, this reaction required heating to 120 °C, as evidence of incomplete electrocyclization was observed after heating to 80 °C for 16 hours.[15]

In conclusion, we have disclosed a new method for the preparation of benzo[*c*]coumarin and phenanthridin-6(5*H*)-one scaffolds *via* a one-pot aldol elimination/6π-electrocyclization/oxidative aromatization reaction cascade. This new metal-free method benefits from high atom economy, a straightforward synthesis of the starting material, and moderate to high yields. By altering the chalcone coupling partner, dibenzofurans and carbazoles can also be prepared in moderate yields using the method described herein. Application of this cascade to other scaffolds is currently underway and will be reported in due course.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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